The importance of the size of erythema migrans (EM) for diagnosis of Lyme borreliosis in Slovenian children

O pomembnosti velikosti erythema migrans (EM) za diagnozo lymske borelioze pri otrocih v Sloveniji

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Abstract

Background: To see how often the largest diameter of EM was less than 5 cm and to compare clinical features and course of the disease in patients with EM < 5 cm and EM ≥ 5 cm.

Methods: 650 patients < 15 years of age referred to our institution from 1996 to 2004 with solitary EM were included in this prospective study. Clinical data were collected by questionnaire. Blood was taken and antibiotics were prescribed. Course of the disease was evaluated by follow-up for at least one year.

Results: 81 patients had EM < 5 cm. At presentation, patients with EM < 5 cm had shorter incubation period, shorter duration of EM, less frequently ring-like EM and more frequently EM on the trunk and limbs. Patients with EM ≥ 5 cm more frequently presented with fatigue and regional lymphadenopathy. Laboratory findings were comparable. In both groups of patients *Borrelia burgdorferi* sensu lato bacteremia was found in 7.6 %. Post-treatment course of the disease was also comparable between the two groups.

Conclusions: In 12.5 % of patients aged < 15 years with solitary EM the largest diameter of skin lesion was less than 5 cm. Despite the differences in clinical features at presentation, the course of the disease in patients with EM < 5 cm and EM ≥ 5 cm was comparable. Thus, from clinical point of view it is not wise to wait until the skin lesion enlarges to 5 cm in diameter, but start appropriate treatment at once to avoid dissemination of borrelial infection.

Izvleček

Izhodišča: Lymska borelioza je infekcijska bolezen, ki se prenaša s klopi in prizadene številne organe v telesu. Povzroča jo bakterija *Borrelia burgdorferi* sensu lato. EM je kožni izpuščaj, ki je za lymsko boreliozo značilen klinični znak. Diagnoza EM je klinična. Osnova za klinično diagnozo EM so merila, ki so jih izdelali v CDC. Po omenjenih merilih mora biti premer EM velik najmanj 5 cm. Za diagnozo lymske borelioze pri bolnikih z EM ni potrebna mikrobiološka potrditev bolezni. Z raziskavo smo želeli ugotaviti, kako pogosto je največji premer EM manjši od 5 cm, in primerjati klinične značilnosti in potek bolezni pri bolnikih z EM < 5 cm in EM ≥ 5 cm.

Metode: V prospektivno klinično raziskavo smo vključili 650 bolnikov, mlajših od 15 let, ki so bili napoteni v našo ustanovo od 1996 do 2004 zaradi solitarnega EM. Diagnozo EM smo ugotovili s pomočjo meril CDC. V raziskavo smo vključili tudi tiste bolnike, pri katerih je bil premer EM < 5 cm, če so imeli v anamnezi podatek o vbodu klopa ali piku insekta na mestu EM, prostem intervalu med vbodom/pikom in nastankom EM in širjenje EM od nastanka do pregleda na kliniki. Klinične podatke o bolnikih smo dobili s pomočjo vprašalnika, ki smo ga izpolnili ob vključitvi v raziskavo za vsakega bolnika posebej. V sakemu bolniku smo odvzeli kri za preiskave in predpisali antibiotik. Potek bolezni in končni izid bolezni (pojav t. i. major pojavov lymske borelioze) smo ocenjevali s pomočjo spremljanja bolnikov vsaj eno leto po vključitvi v raziskavo.

Rezultati: Enainosemdeset (12,5 %) bolnikov je imelo premer EM < 5 cm in 569 (87,5 %) bolnikov EM ≥ 5 cm. Ob prvem pregledu smo ugotovili, da imajo bolniki z EM < 5 cm krajšo inkubacijsko dobo bolezni kot bolniki z EM ≥ 5 cm (srednja vrednost 7 dni proti 14 dni; p = 0,0018), krajše trajanje EM (srednja vrednost 3 dni proti 4 dni; p = 0,0058), manj pogosto izpuščaj v obliki kolobarja (79 % proti 87,7 %; p = 0,0484) ter bolj pogosto izpuščaj na trupu (p = 0,0118) in udih (p = 0,0239) kot bolniki, ki imajo EM ≥ 5 cm. Bolniki z EM ≥ 5 cm so pogosteje navajali utrujenost kot bolniki z EM < 5 cm (0 proti 6,7 %; p = 0,0095). Pri telesnem pregledu smo pri bol-

nikih z EM ≥ 5 cm pogosteje ugotovili povečane področne bezgavke kot pri bolnikih z EM < 5 cm (2,5 proti 14,2 %; p = 0,0053). Rezultati laboratorijskih preiskav so bili primerljivi med skupinama bolnikov. V obeh skupinah bolnikov smo ugotovili bakteriemijo s povzročiteljem *Borrelia burgdorferi* sensu lato v 7,6 %. Potek bolezni in končni izid bolezni se prav tako nista razlikovala med obema skupinama bolnikov. Major pojava lymske borelioze smo ugotovili pri 1 od 76 (1,3 %) bolnikov z EM < 5 cm in pri 8 od 478 (1,7 %) bolnikov z EM ≥ 5 cm, ki so ostali v raziskavi vse opazovalno obdobje.

Zaključki: Pri 12,5 % bolnikov, mlajših od 15 let, s solitarnim EM smo ugotovili največji premer izpuščaja, ki je bil manjši od 5 cm. Kljub razlikam v kliničnih značilnostih ob vključitvi v raziskavo pa je bil potek bolezni pri bolnikih z EM < 5 cm in EM ≥ 5 cm primerljiv. Ob upoštevanju modificiranih meril CDC za diagnozo EM menimo, da ni smiselno čakati z zdravljenjem z antibiotikom, da se premer EM poveča na 5 cm, ker s tem tvegamo razsoj borelijske okužbe.

Introduction

Slovenia is a highly endemic region for Lyme borreliosis (LB), a tick-borne multi-system infectious disease caused by *Borrelia burgdorferi* sensu lato.[1] The most frequent clinical manifestation of the early, localized LB is erythema migrans (EM), the pathognomonic sign of the disease.[2] According to the proposed criteria by the Centres for Disease Control and Prevention (CDC), LB is confirmed in patients with EM in whom the size of the largest diameter of skin lesion is at least five centimetres.[3] It has been reported that in Slovenian children with solitary EM the largest diameter of EM may be less than 5 cm and that the clinical diagnosis of LB in some of these patients is additionally confirmed by isolation of *B. burgdorferi* sensu lato from blood.[4]

In the present study we were interested in how often the largest diameter of EM in Slovenian children with solitary EM is smaller than 5 cm. We compared the clinical features and the course of LB in patients with EM < 5 cm and EM ≥ 5 cm.

Patients and methods

The study was approved by the Medical Ethics Committee at the Ministry of Health of the Republic of Slovenia. Informed consent was obtained from the parents or guardians of all patients. Patients younger than 15 years, referred to our institution from 1996 to 2004 because of solitary EM were included in this prospective clinical study. The diagnosis of EM was established according to the modified criteria proposed by CDC.[5] Patients were divided into two groups with regard to the size of the largest diameter of skin lesion: patients with EM < 5 cm and patients with EM ≥ 5 cm. Data on basic demographic and clinical features were collected by a questionnaire. Haematological, biochemical and microbiological investigations were performed as reported previously.[4] The initial disease [mild (EM + 0 to 1 additional symptom), moderate (EM + 2 to 5 symptoms) and severe (EM + ≥ 6 symptoms)] and the major manifestations of LB were defined according to Steere et al.[6] Patients were treated with oral antibiotics according to the Slovenian recommendations for treatment of children with early LB.[7]

Differences in categorical data were analyzed by Yates corrected χ^2 or Fisher exact test, whereas differences in continuous data were assessed by Kruskal-Wallis test. All P values were 2-tailed; P < 0.05 was considered statistically significant.

Results

Out of 650 patients, 81 (12.5 %) belonged to the group of patients with EM < 5 cm and 569 (87.5 %) to the group of patients with EM ≥ 5 cm (mean largest diameter 3.57 ± 0.74 and 10.95 ± 6.33, respectively). The majority of patients were registered during the warm months. The ratio of patients falling into either of the two groups was similar for all nine years and for all months of each year (Figure 1, 2).

We found many statistically significant differences regarding demographic and clinical features between the two groups (Table 1).

No significant difference between the two groups was found for the presence of associated symptoms. The only exception was fatigue, which was more common in patients with EM ≥ 5 cm. The duration of associated symptoms at the time of inclusion into the study was comparable between the two groups (Table 2).

Table 1: Demographic and clinical features of children with solitary erythema migrans (EM): comparison of patients with EM < 5 cm and EM ≥ 5 cm.

	EM < 5 cm	EM ≥ 5 cm	P
Number of patients	81	569	
Female/male[a]	39/42 (48.1/51.9)	270/299 (47.5/52.5)	0.9988
Age in years			
Mean ± SD	6.16 ± 3.09	6.62 ± 3.47	
Median (range)	5.5 (1–14.5)	6 (0.5–14.5)	0.2635
Previous LB[a]	5 (6.2)	43 (7.6)	0.8269
Bite[a,b]			
Tick	57 (70.4)	333 (58.5)	0.0554
Insect	14 (17.3)	40 (7)	0.0036
None	10 (12.3)	196 (34.5)	0.0001
Incubation[c]			
Number of patients	60	297	
Mean ± SD	10.15 ± 11.01	17.79 ± 18.17	
Median (range)	7 (0–60)	14 (0–147)	0.0018
Location of bite[a]			
Head and neck	9 (13.4)	115 (32.7)	0.0026
Trunk	36 (53.8)	152 (43.2)	0.1450
Limbs	22 (32.8)	85 (24.1)	0.1796
Location of EM[a]			
Head and neck	9 (11.1)	191 (33.6)	0.0001
Trunk	40 (49.4)	226 (39.7)	0.0118
Limbs	32 (39.5)	152 (26.7)	0.0239
Duration of EM[d]			
Mean ± SD	3.94 ± 3.71	7.22 ± 10.56	
Median (range)	3 (0–21)	4 (0–88)	0.0058
Shape of EM[a]			
Ring-like	64 (79)	499 (87.7)	0.0484
Homogenous redness	17 (21)	70 (12.3)	

[a] *number of patients (%);* [b] *recent bite at the site of the later EM;* [c] *days from bite to the time when EM was first noticed by the patient;* [d] *days (duration of EM as noticed by patient) prior to enrolment; LB: Lyme borreliosis*

Table 2: Associated symptoms in children with solitary erythema migrans (EM): comparison of patients with EM < 5 cm and EM ≥ 5 cm.

[a] *number of patients (%)*

	EM < 5 cm	EM ≥ 5 cm	P
Number of patients	81	569	
Symptoms[a]	34 (42)	292 (51.3)	0.1458
Local symptoms[a]	26 (32.1)	222 (39)	0.2816
Number of events (%)			
Itching	26 (32.1)	200 (35.1)	0.6784
Pain	2 (2.5)	43 (7.6)	0.1460
Burning	0	15 (2.6)	0.2371
Prickling	0	3 (0.5)	1.0000
Systemic symptoms[a]	15 (18.5)	140 (24.6)	0.2877
Number of events (%)			
Fatigue	0	38 (6.7)	0.0095
Malaise	1(1.2)	16 (2.8)	0.7095
Fever	3 (3.7)	38 (6.7)	0.4318
Headache	4 (4.9)	61 (10.7)	0.1541
Dizziness	1 (1.2)	4 (0.7)	0.4871
Nausea	0	12 (2.1)	0.3788
Myalgia	3 (3.7)	10 (1.8)	0.2132
Skeletal pain	1 (1.2)	3 (0.5)	0.4136
Arthralgia	1 (1.2)	21 (3.7)	0.5025
Irritability	1 (1.2)	9 (1.6)	1.0000
Paresthesia	0	1 (0.2)	1.0000
Sore throat	2 (2.5)	6 (1.1)	0.2622
Vomiting	2 (2.5)	8 (1.4)	0.3600
Abdominal pain	2 (2.5)	7 (1.2)	0.3114
Sleepiness	2 (2.5)	3 (0.5)	0.1194
Behaviour changes	1 (1.2)	3 (0.5)	0.4136
Insecure gait	0	1 (0.2)	1.0000
Initial disease[a]			
Mild	69 (85.2)	451 (79.3)	0.2984
Moderate	11 (13.6)	115 (20.2)	0.0883
Severe	1 (1.2)	3 (0.5)	0.4468
Duration of symptoms (days)			
Number of patients	34	286	
Mean ± SD	3.82 ± 4.43	5.65 ± 7.92	
Median (range)	2 (1–21)	3 (0–60)	0.1872
Duration of local symptoms (days)			
Number of patients	26	214	
Mean ± SD	3.42 ± 4.08	5.62 ± 8.06	
Median (range)	2 (1–21)	3 (0–60)	0.1390
Duration of systemic symptoms (days)			
Number of patients	15	136	
Mean ± SD	3.93 ± 4.25	5.14 ± 6.62	
Median (range)	2 (1–17)	2.5 (0–44)	0.4913

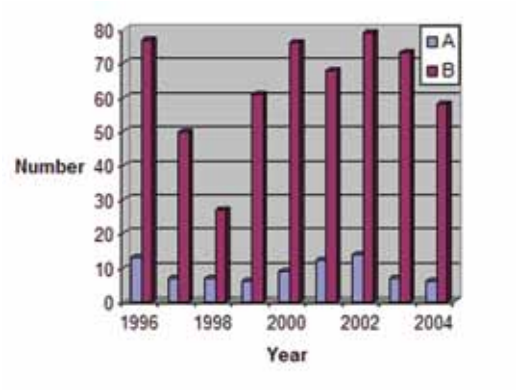

Figure 1 (left): Year of registration of patients with solitary erythema migrans (EM): comparison of patients with EM < 5 cm (A) and EM ≥ 5 cm (B).

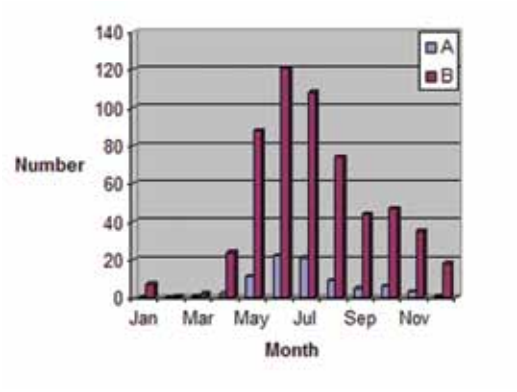

Figure 2 (right): Month of registration of patients with solitary erythema migrans (EM): comparison of patients with EM < 5 cm (A) and EM ≥ 5 cm (B).

At physical examination, pathological clinical status was more often observed in patients with EM ≥ 5 cm (Table 3).

No significant difference was found for the presence of abnormal laboratory findings between the two groups, however, the time intervals between the bite and blood culturing and the appearance of EM and blood culturing were significantly shorter in patients with EM < 5 cm (Table 4).

Out of 81 patients with EM < 5 cm and 569 with EM ≥ 5 cm, 76 (93.8 %) and 478 (84 %) were followed-up for at least one year after inclusion into the study (p = 0.0305). The course of the disease is shown in Table 5.

Discussion

LB in Slovenia is endemic and EM is by far the most common manifestation recorded.[1] According to the CDC surveillance definition, solitary EM is a round or oval expanding skin lesion at the site of tick bite and should be at least 5 cm in larger diameter for secure diagnosis.[8,9] In this article we report the findings from a clinical evaluati-

Table 3: Clinical signs at the time of enrolment in patients with solitary erythema migrans (EM): comparison of patients with EM < 5 cm and EM ≥ 5 cm.

	EM < 5 cm	EM ≥ 5 cm	P
Number of patients	81	569	
Clinical findings other then EM[a]	11 (13.6)	151 (26.5)	0.0171
Number of events (%)			
Regional lymphadenopathy	2 (2.5)	81 (14.2)	0.0053
Generalized lymphadenopathy	0	6 (1.1)	1.0000
Conjunctivitis	2 (2.5)	11 (1.9)	0.6707
Erythematous throat	5 (6.2)	38 (6.7)	0.9461
Enlarged liver	1 (1.2)	8 (1.4)	1.0000
Enlarged spleen	1 (1.2)	9 (1.6)	1.0000
Body temperature ≥ 38°C	0	9 (1.6)	0.6109
Positive meningeal signs	0	4 (0.7)	1.0000
Positive Romberg's sign	0	1 (0.2)	1.0000
Painful muscles	0	1 (0.2)	1.0000
Painful spine	0	1 (0.2)	1.0000
Reduced limb mobility	0	1 (0.2)	1.0000

[a] *number of patients (%)*

on of 650 Slovenian patients younger than 15 years with solitary EM, using modified criteria for diagnosis proposed by CDC.[5] Patients with EM lesions less than 5 cm in diameter (12.5 %) were also enrolled.

The comparison of 81 patients with EM < 5 cm and 569 with EM ≥ 5 cm showed many similarities but also differences in clinical features and course of LB between the two groups.

By rule, the diagnosis of EM can be made on the basis of its clinical appearance alone and on evolution of the erythema.[10] EM is the only manifestation of Lyme disease in U.S.A. that allows diagnosis without laboratory confirmation.[9] In a patient with a compatible epidemiologic and clinical history, the preferred means of diagnosis is visual inspection of the skin lesion.[9]

The results of the present study support the knowledge that LB is an endemic disease in Slovenia and that the onset of the disease is seasonally associated with the activity of *Ixodes ricinus*.[1] As has been expected, the majority of patients were registered during summer months, regardless of the size of EM (Figure 2). In both groups of patients boys predominated but the difference was not significant. Age of the patients was also comparable (Table 1).

EM may appear on almost any part of the body.[10] Compared to patients with EM ≥ 5 cm, our patients with EM < 5 cm were less frequently bitten on head and neck and had

Table 4: Abnormal laboratory findings, borrelial serum antibody titres and blood culture results in patients with solitary erythema migrans (EM): comparison of patients with EM < 5 cm and EM ≥ 5 cm.

Laboratory findings[a]	EM < 5 cm	EM ≥ 5 cm	P
ESR > 20 mm/h	10/73 (13.7)	61/527 (11.6)	0.7390
L > 10 x 10^9/L	7/81 (8.6)	31/559 (2.5)	0.3095
L < 4 x 10^9/L	2/81 (2.5)	14/559 (2.5)	1.0000
Ptl < 140 x 10^9/L	1/81 (1.2)	5/556 (0.9)	0.5593
Bil > 17 mmol/L	0/79	21/540 (3.9)	0.0940
ALT > 0.6 µkat/L	1/79 (1.3)	6/549 (1.1)	1.0000
AST > 0.6 µkat/L	7/79 (8.9)	27/551 (4.9)	0.1767
IFA antibody titres[a]			
IgM ³ 1 : 256	1/81 (1.2)	12/569 (2.1)	1.0000
IgG ³ 1 : 256	2/81 (2.5)	27/569 (4.7)	0.5636
IgM + IgG ³ 1 : 256	0	7/569 (1.2)	0.6051
B. burgdorferi sensu lato in blood[a]	6/79 (7.6)	41/540 (7.6)	0.8207
Days from bite to blood culturing			
Number of patients	66	329	
Mean ± SD	15.52 ± 13.52	24.91 ± 22.17	
Median (range)	10 (1–62)	18 (0–160)	0.0010
Days from appearance of EM to blood culturing			
Number of patients	79	540	
Mean ± SD	3.92 ± 3.76	7.27 ± 10.73	
Median (range)	3 (0–21)	4 (0–88)	0.0062

[a] *number of abnormal findings/number of examined patients (%); ESR: erythrocyte sedimentation rate; L: leukocytes; Plt: platelets; Bil: bilirubin; ALT: alanin transaminase; AST: aspartate transaminase; IFA: immunofluorescent assay to B. afzelii*

Table 5: Course of the disease during one year follow-up after inclusion into the study in patients with solitary erythema migrans (EM): comparison of patients with EM < 5 cm and EM ≥ 5 cm.

	EM < 5 cm	EM ≥ 5 cm	P
Antibiotic[a]			
phenoxymethylpenicillin	24 (29.6)	180 (31.7)	0.8382
clarithromycin	2 (2.5)	28 (4.9)	0.5678
azithromycin	25 (30.9)	191 (33.6)	0.7209
cefuroxime axetil	15 (18.5)	69 (12)	0.1374
amoxicillin	15 (18.5)	101 (17.8)	0.9889
"Jarisch-Herxheimer's" reaction[a]	7/81 (8.6)	72/565 (12.7)	0.3830
Local	7/81 (8.6)	66/565 (11.7)	0.5350
Systemic	0	13/565 (2.3)	0.3881
Duration of EM (days)			
Number of patients	81	565	
Mean ± SD	6.68 ± 6.73	5.68 ± 8.35	
Median (range)	4 (1–40)	3 (1–120)	0.3036
Duration of symptoms (days)			
Number of patients	11	129	
Mean ± SD	6.91 ± 6.25	7.76 ± 16.23	
Median (range)	5 (1–17)	3 (1–150)	0.5543
Duration of local symptoms (days)			
Number of patients	5	73	
Mean ± SD	6.8 ± 6.69	3.16 ± 4.25	
Median (range)	4 (1–14)	2 (1–32)	0.0782
Duration of systemic symptoms (days)			
Number of patients	9	85	
Mean ± SD	6.78 ± 6.18	10.34 ± 19.45	
Median (range)	5 (1–17)	7 (1–150)	0.2804
Major manifestations[a]	1/76 (1.3)[b]	8/478 (1.7)[c]	1.0000
New EM[a]	0/76	8/478 (1.7)	0.6067
Hospitalization[a]	2/76 (2.6)	72/478 (6.7)	0.2068

[a] *number of patients (%);* [b] *arthritis;* [c] *meningitis (1), peripheral facial palsy (2), peripheral facial palsy and meningitis (1), multiple EM (3), multiple EM and meningitis (1)*

EM more frequently located on the trunk and limbs . Furthermore, the patients with EM < 5 cm were more frequently bitten by insects (Table 1). It is reported that hypersensitivity reactions to bite are usually < 5 cm in the largest diameter and typically begin to disappear within 24–48 hours. In contrast, an early solitary EM lesion usually increases in size, so observation for this time frame without antibiotic therapy is suggested.[9] Our patients with EM < 5 cm were included only if they recalled a recent bite at the site of EM, had a symptoms-free interval between the bite and the onset of EM, and/

or reported an expanding skin lesion prior to diagnosis.[5]

EM usually develops at the site of deposition of *B. burgdorferi* sensu lato by tick. The skin lesion becomes apparent approximately 7–14 days after the tick detachment or removal.[9] Incubation period in our patients was significantly longer in patients with EM ≥ 5 cm (Table 1). Longer incubation period is reported in children with multiple EM, an early disseminated LB, compared to those with solitary EM, an early localized LB.[11] Longer incubation of the disease may be associated with local and/or systemic spreading of *B. burgdorferi* sensu lato before symptoms and signs of the disease are first noticed by the patient.

EM is the hallmark of LB.[10] The initial lesion is usually homogenous and it sometimes remains unchanged until it heals. However, the majority of the lesions partly or totally clear centrally, leaving an annular EM which spreads centrifugally.[10] Sometimes it can have a distinctive target-like appearance.[10] The medium size of EM and skin lesion area increases with increasing duration of the lesion.[10,12,13] Our patients with EM < 5 cm had shorter duration of EM at presentation and showed less likely central clearing of skin lesions, an appearance typically associated with older skin lesions (Table 1).

In the present study, a mean diameter of EM lesions for all 650 patients included was 10.03 ± 6.41 cm, 8.5 (1–73), however, the duration of EM [6.81 ± 10.21 days, 4 (0–88)] at presentation was comparable to the report of U.S. adult patients.[12] Although the duration of EM is similar, the size of EM in adult patients from U.S.A. is larger than in our paediatric patients.[12,15] The comparison of adult patients with EM from Europe and U.S.A. shows that despite the longer duration of EM at presentation in Slovenian patients, the size of skin lesions (3.5 % with EM < 5 cm) is similar, implying that *B. afzelii* spreads more slowly in the skin as does *B. burgdorferi* sensu stricto.[15] Our results support this hypothesis since *B. afzelii* is also the main causative agent of EM in Slovenian children.[11] The size of EM at presentation seems to be larger in adults than in children, however this applies only to adult patients from U.S.A.[12,14,15]

EM is frequently accompanied by "flu-like" symptoms and these symptoms may be the presenting manifestation of the disease.[2] Steere defined the initial disease as mild, moderate or severe according to the number of associated symptoms.[6] Symptoms often develop independently of EM.[12] We also couldn't demonstrate a correlation between the severity of disease and the duration of EM. Although the duration of skin lesion was longer in patients with EM ≥ 5 cm, the severity of disease was comparable between the two groups. However, patients with EM ≥ 5 cm more often complained of fatigue (Table 2). Regional lymph nodes were also more frequently enlarged in these patients, which is probably the consequence of longer duration of EM prior to treatment (Table 3). In most patients laboratory findings were normal and no difference was observed between the two groups (Table 4).

European studies report low rates of seropositivity in patients with EM.[15] Our results support previous findings about deficiency in serological response.[11,13] Despite a longer incubation period and longer duration of EM at presentation in patients with EM ≥ 5 cm, positive borrelial serum antibody titres were comparable to those in patients with EM < 5 cm (Table 4).

Culturing of blood for isolation of *B. burgdorferi* sensu lato is not recommended for the diagnosis of EM in routine clinical care.[9] In U.S. adult patients with EM certain subspecies of *B. burgdorferi* sensu stricto are associated with bloodstream invasion.[16] The size of EM does not correlate with bacteremia and the risk for bacteremia in patients with solitary EM is not related to a larger surface area of infected skin.[16] Multiple skin lesions, younger age and male sex are identified as possible risk factors for bloodstream invasion of *B. burgdorferi* sensu lato in Slovenian children. *B. afzelii* is the most frequent isolate from blood.[11] In a recent report, approximately 9 % of children with solitary EM have the largest diameter of skin lesion < 5 cm; 25 % of these patients have isolation of *B. burgdorferi* sensu lato from blood.[4] In present study, the rate of isolation of

B. burgdorferi sensu lato from blood in both groups of patients was 7.6 % despite shorter intervals between the bite and blood culturing and between the appearance of EM and blood culturing in patients with EM < 5 cm (Table 4). An early onset and prolonged duration of risk for bacteremia are observed in untreated adult U.S. patients and Slovenian children with EM.[16,17] The results of our study support this observation.

Prompt institution of appropriate antibiotic therapy is warranted to avoid dissemination of *B. burgdorferi* sensu lato to anatomic sites beyond the lesion site.[16,17] An untreated EM generally disappears within a few weeks to months.[10] Antibiotic treatment shortens the course of EM and prevents late manifestations of LB.[5-7] If EM does not heal after adequate antibiotic therapy, the diagnosis of EM should be reconsidered.[10] The proportions of our patients treated with different antibiotics were similar in both groups and exacerbation of EM and/or worsening of systemic symptoms and signs at the beginning of antibiotic treatment ("Jarisch--Herxeimer's" reaction) were comparable (Table 5). Skin lesions resolved completely, without recurrence, in all patients. The duration of EM and associated symptoms after treatment was comparable between the two groups (Table 5).

The major manifestations of LB were evaluated in patients who remained in the study through one-year observational period. The duration of EM before treatment often seems to be shorter in patients who develop extracutaneous complications of LB.[10] In the present study, the major manifestations of LB were detected in 1.3 % of patients with EM < 5 cm and 1.7 % of patients with EM ≥ 5 cm (p = 1.0000), despite the significantly different duration of EM prior to treatment.

CDC definition for diagnosis of EM is useful in clinical and epidemiological studies, but may be too restrictive in evaluating individual patients.[13] This is especially true for evaluating a child with skin lesion < 5 cm, otherwise typical for EM.

In conclusion, this prospective clinical study demonstrates that 12.5 % of Slovenian patients younger than 15 years with solitary EM have the largest diameter of skin lesion less than 5 cm. Despite differences in clinical features at presentation, the course of the disease in patients with EM < 5 cm and EM ≥ 5 cm is comparable. Thus, from the clinical point of view, it is not wise to wait until the skin lesion enlarges to 5 cm in diameter, but start appropriate treatment at once to avoid dissemination of borrelial infection.

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